

Please amend the application as follows:

**Amendments to the Claims:**

This listing of the claims will replace all prior versions, and listings, of claims in the application:

**Listing of the Claims:**

**Claims 1-67 (Cancelled)**

68. (Currently Amended) A therapeutic agent suitable for administration in vivo comprising an entity having a therapeutic property covalently linked to an exogenous surface loop of 4-20 amino acids that specifically binds to a target, said entity retaining its therapeutic property and said surface loop retaining a specific binding characteristic for said target, wherein said exogenous loop replaces a removed surface loop in said entity or is inserted between two regions of secondary structure in said entity or between a domain of secondary structure and a terminus of said entity.

69. (Previously presented) The therapeutic agent of claim 68 wherein the exogenous surface loop is optimized to increase its natural affinity for the target.

70. (Previously presented) The therapeutic agent of claim 68 wherein the target is selected from the group consisting of: a tissue, an organ, a cell, a virus, an organelle, and a microorganism.

71. (Currently Amended) The therapeutic agent of claim 68 wherein the target is selected from the group consisting of: a synthetic or naturally occurring molecule, a peptide, a protein, a lipid, a carbohydrate, a nucleic acid, a glycoprotein, a phosphoprotein, a glycolipid, a hormone, a transcription factor, a kinase, a phosphatase, any protein found in the blood, an adhesive protein, a component of the extracellular matrix, a receptor or other cell surface protein, an albumin, an IgG-like molecule, a soluble protein, an antibody, a growth factor, a cytokine, a modulator of angiogenesis, a cell surface protein, an integrin, a cadherin, a growth factor receptor, a proteoglycan, a member of the seven-membrane spanner protein family, an odorant or taste receptor of the seven-membrane spanner protein family, a ligand-dependent receptor, a steroid receptor, a thyroid hormone receptor, a retinoic acid receptor, a retinoid X receptor, TCCD (dioxin) receptor, a fatty acid activatable receptor, and the acetylcholine receptor.

72. (Currently Amended) The therapeutic agent of claim 68 wherein the target is selected from the group consisting of: a blood clot, a tumor, an aneurism, an atherosclerotic plaque, metastatic cells, cells of the vasculature, endothelial cells of the vasculature, smooth muscle cells of the vasculature, cells of the lungs, muscle, cardiac muscle, cells of the kidneys, a blood cell, a T-cell, cells of the bone marrow, stem cells of the bone marrow, cells of bone, neurons and related neurological cells, glial cells, brain cells, liver cells, precursors of cells, a proteoglycan, and an ion channel.

73. (Withdrawn) The therapeutic agent of claim 72 wherein the target is a blood cell or a T-cell.

74. (Previously presented) The therapeutic agent of claim 71 wherein the target is a cell surface protein.

75. (Previously presented) The therapeutic agent of claim 74 wherein the cell surface protein is an integrin.

76. (Withdrawn) The therapeutic agent of claim 74 wherein the cell surface protein is a soluble protein.

77. (Previously presented) The therapeutic agent of claim 75 wherein the integrin is  $\alpha_{\text{IIb}}\beta_3$ , integrin  $\alpha_v\beta_3$ , or integrin  $\alpha_v\beta_5$ .

78. (Previously presented) The therapeutic agent of claim 77 wherein the integrin  $\alpha_{\text{IIb}}\beta_3$ .

79. (Withdrawn) The therapeutic agent of claim 70 wherein the cell is a tumor cell or a metastatic cell.

80. (Previously presented) The therapeutic agent of claim 75 wherein the integrin binds to an Arg-Gly-Asp (RGD) tripeptide motif.

81. (Previously presented) The therapeutic agent of claim 68 wherein the agent having a therapeutic property is selected from the group consisting of: an enzyme, a thrombolytic agent, an anticoagulant, an apoptotic protein, a growth factor, a cytokine, a chemotherapeutic agent, and a cell surface receptor ligand.

82. (Currently amended) The therapeutic agent of claim 68 wherein the entity is selected from the group consisting of a nucleic acid, a protein, a peptide, a gene delivery vehicle, a plasmid, a virus, a liposome complex, a synthetic or naturally occurring enzyme, a protease, a

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phosphatase, a kinase, a P450, a drug metabolizing enzyme, superoxide dismutase, nitric oxide synthase, a thrombolytic agent, tissue plasminogen activator, uPA, vampire bat tPA, staphylokinase, streptokinase, an acylated streptokinase-plasminogen complex, an anticoagulant, an inhibitor of a member of the blood coagulation cascade, an antagonist of an integrin adhesion receptor, protein C or activated protein C, tissue factor pathway inhibitor, Factor VII, Factor X, thrombin, an inhibitor of platelet function, an inhibitor of Factor XIII, a compound that inhibits the activity of a protein involved in blood coagulation, heparin, a chemotherapeutic agent, doxyrubicin, an apoptotic agent, a pharmaceutical, a growth factor, a cytokine, a ligand for a cell surface receptor, a carbohydrate, a lipid, a miniaturized osmotic drug delivery pump, an imaging agent, a radiochemical, a fluorescent chemical, and a metal ion.

83. (Withdrawn) The therapeutic agent of claim 82 wherein the entity is a chemotherapeutic agent, and the chemotherapeutic agent is doxyrubicin.

84. (Previously presented) The therapeutic agent of claim 68 wherein the therapeutic agent is a recombinant protein.

85. (Withdrawn) The therapeutic agent of claim 68 wherein the therapeutic agent is an antibody or IgG-like protein.

86. (Previously presented) The therapeutic agent of claim 68 wherein the entity is a synthetic or naturally occurring peptide or protein.

87. (Previously presented) The therapeutic agent of claim 68 wherein the exogenous surface loop is a complementarity determining region of a monoclonal antibody molecule.

88. (Previously presented) The therapeutic agent of claim 87 wherein the complementarity determining region is heavy chain complementarity determining region 3 (HCDR3) of monoclonal antibody Fab-9.

89. (Previously presented) The therapeutic agent of claim 68 wherein the exogenous surface loop is the HCDR3 of monoclonal antibody Fab-9, the entity having a therapeutic property is tissue type plasminogen activator (tPA) or a variant of tissue type plasminogen activator, and the target is selected from the group consisting of: integrin  $\alpha_{IIb}\beta_3$ , integrin  $\alpha_v\beta_5$ , and integrin  $\alpha_v\beta_3$ .

90. (New) The therapeutic agent of claim 68 wherein the target is selected from the group consisting of: a lipid, a carbohydrate, a nucleic acid, a phosphoprotein, a glycolipid, a

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hormone, a transcription factor, a kinase, a phosphatase, an adhesive protein, a component of the extracellular matrix, an albumin, a growth factor, a cytokine, a modulator of angiogenesis, an integrin, a cadherin, a growth factor receptor, a proteoglycan, a member of the seven-membrane spanner protein family, an odorant or taste receptor of the seven-membrane spanner protein family, a steroid receptor, a thyroid hormone receptor, a retinoic acid receptor, a retinoid X receptor, TCCD (dioxin) receptor, a fatty acid activatable receptor, and the acetylcholine receptor.

91. (New) The therapeutic agent of claim 68 wherein the entity is selected from the group consisting of a nucleic acid, a gene delivery vehicle, a plasmid, a virus, a liposome complex, a synthetic or naturally occurring enzyme, a protease, a phosphatase, a kinase, a P450, a drug metabolizing enzyme, superoxide dismutase, nitric oxide synthase, a thrombolytic agent, tissue plasminogen activator, uPA, vampire bat tPA, staphylokinase, streptokinase, an acylated streptokinase-plasminogen complex, an anticoagulant, an inhibitor of a member of the blood coagulation cascade, an antagonist of an integrin adhesion receptor, protein C or activated protein C, tissue factor pathway inhibitor, Factor VII, Factor X, thrombin, an inhibitor of platelet function, an inhibitor of Factor XIII, a compound that inhibits the activity of a protein involved in blood coagulation, heparin, a chemotherapeutic agent, doxorubicin, an apoptotic agent, a pharmaceutical, a growth factor, a cytokine, a ligand for a cell surface receptor, a carbohydrate, a lipid, a miniaturized osmotic drug delivery pump, an imaging agent, a radiochemical, a fluorescent chemical, and a metal ion.